volume by enhancing renal tubular reabsorption of sodium, resulting in the excretion of a low-volume, concentrated, sodium-free urine. Vasopressin has a direct action on vascular smooth muscle, contributing to vasoconstriction, and acts on the distal renal tubules to enhance water reabsorption.

### CARDIOVASCULAR RESPONSE

Three variables—ventricular filling (preload), the resistance to ventricular ejection (afterload), and myocardial contractility—are paramount in controlling stroke volume (Chap. 265e). Cardiac output, the major determinant of tissue perfusion, is the product of stroke volume and heart rate. Hypovolemia leads to decreased ventricular preload that, in turn, reduces the stroke volume. An increase in heart rate is a useful but limited compensatory mechanism to maintain cardiac output. A shock-induced reduction in myocardial compliance is frequent, reducing ventricular end-diastolic volume and, hence, stroke volume at any given ventricular filling pressure. Restoration of intravascular volume may return stroke volume to normal but only at elevated filling pressures. Increased filling pressures stimulate release of brain natriuretic peptide (BNP) to secrete sodium and volume to relieve the pressure on the heart. Levels of BNP correlate with outcome following severe stress. In addition, sepsis, ischemia, myocardial infarction (MI), severe tissue trauma, hypothermia, general anesthesia, prolonged hypotension, and acidemia may all also impair myocardial contractility and reduce the stroke volume at any given ventricular end-diastolic volume. The resistance to ventricular ejection is significantly influenced by the systemic vascular resistance, which is elevated in most forms of shock. However, resistance is decreased in the early hyperdynamic stage of septic shock or neurogenic shock (Chap. 325), thereby initially allowing the cardiac output to be maintained or elevated.

The venous system contains nearly two-thirds of the total circulating blood volume, most in the small veins, and serves as a dynamic reservoir for autoinfusion of blood. Active venoconstriction as a consequence of α-adrenergic activity is an important compensatory mechanism for the maintenance of venous return and, therefore, of ventricular filling during shock. By contrast, venous dilation, as occurs in neurogenic shock, reduces ventricular filling and hence stroke volume and potentially cardiac output.

### PULMONARY RESPONSE

The response of the pulmonary vascular bed to shock parallels that of the systemic vascular bed, and the relative increase in pulmonary vascular resistance, particularly in septic shock, may exceed that of the systemic vascular resistance, leading to right heart failure. Shock-induced tachypnea reduces tidal volume and increases both dead space and minute ventilation. Relative hypoxia and the subsequent tachypnea induce a respiratory alkalosis. Recumbency and involuntary restriction of ventilation secondary to pain reduce functional residual capacity and may lead to atelectasis. Shock and, in particular, resuscitation-induced reactive oxygen species (oxidant radical) generation are recognized as major causes of acute lung injury and subsequent acute respiratory distress syndrome (ARDS; Chap. 322). These disorders are characterized by noncardiogenic pulmonary edema secondary to diffuse pulmonary capillary endothelial and alveolar epithelial injury, hypoxemia, and bilateral diffuse pulmonary infiltrates. Hypoxemia results from perfusion of underventilated and nonventilated alveoli. Loss of surfactant and lung volume in combination with increased interstitial and alveolar edema reduces lung compliance. The work of breathing and the oxygen requirements of respiratory muscles increase.

### RENAL RESPONSE

Acute kidney injury (Chap. 334), a serious complication of shock and hypoperfusion, occurs less frequently than heretofore because of early aggressive volume repletion. Acute tubular necrosis is now more frequently seen as a result of the interactions of shock, sepsis, the administration of nephrotoxic agents (such as aminoglycosides and angiographic contrast media), and rhabdomyolysis; the latter may be particularly severe in skeletal muscle trauma. The physiologic response of the kidney to hypoperfusion is to conserve salt and water. In addition to decreased renal blood flow, increased afferent arteriolar resistance accounts for diminished glomerular filtration rate (GFR) that, together with increased aldosterone and vasopressin, is responsible for reduced urine formation. Toxic injury causes necrosis of tubular epithelium and tubular obstruction by cellular debris with back leak of filtrate. The depletion of renal ATP stores that occurs with prolonged renal hypoperfusion contributes to subsequent impairment of renal function.

### METABOLIC DERANGEMENTS

During shock, there is disruption of the normal cycles of carbohydrate, lipid, and protein metabolism. Through the citric acid cycle, alanine in conjunction with lactate, which is converted from pyruvate in the periphery in the presence of oxygen deprivation, enhances the hepatic production of glucose. With reduced availability of oxygen, the breakdown of glucose to pyruvate, and ultimately lactate, represents an inefficient cycling of substrate with minimal net energy production. An elevated plasma lactate/pyruvate ratio is preferable to lactate alone as a measure of anaerobic metabolism and reflects inadequate tissue perfusion. Decreased clearance of exogenous triglycerides coupled with increased hepatic lipogenesis causes a significant rise in serum triglyceride concentrations. There is increased protein catabolism as energy substrate, a negative nitrogen balance, and, if the process is prolonged, severe muscle wasting.

### INFLAMMATORY RESPONSES

Activation of an extensive network of proinflammatory mediator pathways by the innate immune system plays a significant role in the progression of shock and contributes importantly to the development of multiple organ injury, multiple organ dysfunction (MOD), and MOF (Fig. 324-2). In those surviving the acute insult, there is a prolonged endogenous counterregulatory response to "turn off" or balance the excessive proinflammatory response. If balance is restored, the patient does well. If the response is excessive, adaptive immunity is suppressed and the patient is highly susceptible to secondary nosocomial infections, which may then drive the inflammatory response and lead to delayed MOF.

Multiple humoral mediators are activated during shock and tissue injury. The complement cascade, activated through both the classic and alternate pathways, generates the anaphylatoxins C3a and C5a (Chap. 372e). Direct complement fixation to injured tissues can progress to the C5-C9 attack complex, causing further cell damage. Activation of the coagulation cascade (Chap. 141) causes microvascular thrombosis, with subsequent fibrinolysis leading to repeated episodes of ischemia and reperfusion. Components of the coagulation system (e.g., thrombin) are potent proinflammatory mediators that cause expression of adhesion molecules on endothelial cells and activation of neutrophils, leading to microvascular injury. Coagulation also activates the kallikrein-kininogen cascade, contributing to hypotension.

Eicosanoids are vasoactive and immunomodulatory products of arachidonic acid metabolism that include cyclooxygenase-derived prostaglandins (PGs) and thromboxane $A_2$, as well as lipoxygenase-derived leukotrienes and lipoxins. Thromboxane $A_2$ is a potent vasoconstrictor that contributes to the pulmonary hypertension and acute tubular necrosis of shock. $PGI_2$ and $PGE_2$ are potent vasodilators that enhance capillary permeability and edema formation. The cysteinyl leukotrienes $LTC_4$ and $LTD_4$ are pivotal mediators of the vascular sequelae of anaphylaxis, as well as of shock states resulting from sepsis or tissue injury. $LTB_4$ is a potent neutrophil chemoattractant and secretagogue that stimulates the formation of reactive oxygen species. Platelet-activating factor, an ether-linked, arachidonyl-containing phospholipid mediator, causes pulmonary vasoconstriction, bronchoconstriction, systemic vasodilation, increased capillary permeability, and the priming of macrophages and neutrophils to produce enhanced levels of inflammatory mediators.

Tumor necrosis factor α (TNF-α), produced by activated macrophages, reproduces many components of the shock state, including